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Diffuse proliferative lupus nephritis: Identification of specific pathologic features affecting renal outcome

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Diffuse proliferative lupus nephritis: Identification of specific pathologic features affecting renal outcome. Prerandomization renal biopsy specimens were examined in 102 patients upon entry into prospective therapeutic trials of lupus nephritis in an attempt to identify early predictors of renal failure outcome. All 11 renal failures occurred among the 72 individuals with diffuse proliferative or membranoproliferative glomerulonephritis (DPGN/MPGN); thus, these patients were at modestly, but significantly, increased risk of endstage renal disease compared to those with focal proliferative, membranous, or mesangial glomerulonephritis. Considering the low incidence of endstage renal disease among patients with DPGN/MPGN, we sought to refine the prognostic information obtained from renal morphology by semiquantitative scoring of individual histologic features and by derivation of composite histologic scores specified by Activity (AI) and Chronicity (CI) Indices. Among the 72 patients with DPGN/MPGN, the composite AI was more strongly predictive of renal failure than were the individual active histologic features; cellular crescents and extensive fibrinoid necrosis yielded positive associations, while endocapillary proliferation, leucocytic exudation, and hyaline thrombi in glomeruli and interstitial inflammation by themselves did not emerge as useful prognostic indicators. However, chronicity items (glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis) considered individually, as well as in the composite CI, were highly predictive of renal failure outcome. Particularly striking was the prognostic value of tubular atrophy; all 11 renal failures were among the 43 patients with tubular atrophy on prerandomization renal biopsy. While no single pathologic variable improved outcome predictions among those with tubular atrophy, examination for interactions among variables revealed that glomerular sclerosis and cellular crescents had a synergistic effect which augmented the prognostic information derived from analysis of tubular atrophy alone. Thus, the simultaneous occurrence of tubular atrophy, glomerular sclerosis, and cellular crescents identified a very high-risk group; six of nine patients progressed to endstage renal disease within 4 years of study entry. In conclusion, semiquantitative scoring of individual histologic features can refine estimates of the risk of renal failure in lupus patients with DPGN or MPGN.

Néphrite lupique proliférative diffuse: Identification de caractéristiques pathologiques spécifiques affectant l'évolution rénale. Les spécimens biopsies rénales de 102 malades avant randomisation ont été examinées à l'entrée dans des essais thérapeutiques prospectifs de la néphrite lupique, destinés à identifier les facteurs prédictifs précoces de survenue d'une insuffisance rénale. La totalité des 11 insuffisances rénales est survenue parmi les 72 sujets atteints d'une glomérulonéphrite diffuse proliférative ou membrano-proliférative (DPGN/MPGN); ainsi, ces malades avaient un risque modérément, mais significativement, accru de néphropathie terminale, par rapport à ceux atteints d'une glomérulonéphrite proliférative focale, extramembraneuse ou mésangiale. En considérant la faible incidence d'une néphropathie terminale parmi les patients atteints de DPGN/MPGN, nous avons cherché à affiner l'information pronostique obtenue à partir de la morphologie rénale par un score semiquantitatif des caractéristiques histologiques individuelles et par des scores histologiques composites dérivés spécifiés par des Index d'Activité (AI) et de Chronicité (CI). Parmi les 72 malades atteints de DPGN/MPGN, l'AI composite était plus fortement prédictif d'une insuffisance rénale que les caractéristiques histologiques actives individuelles; les croissants cellulaires et une nécrose fibrinoïde étendue donnaient des associations positives, alors que la prolifération endocapillaire, l'exsudation leucocytaire et des thrombus hyalins dans les glomérules, ainsi que l'inflammation interstitielle en eux-mêmes, n'apparaîssaient pas comme des indicateurs utiles de pronostic. Cependant, les items de chronicité (sclérose glomérulaire, croissants fibreux, atrophie tubulaire, et fibrose interstitielle) considáerés individuellement, ainsi que dans le CI composite, étaient hautement prédictifs de la survenue d'une insuffisance rénale. Particulièrement frappante était la valeur pronostique de l'atrophie tubulaire; les 11 insuffisances rénales étaient parmi les 43 malades ayant une atrophie tubulaire à la biopsie ráenale prérandomisation. Alors qu'aucune variable pathologique isolée n'améliorait les prédictions sur le devenir parmi ceux atteints d'atrophie tubulaire, l'examen des interactions entre variables a révélé que la sclérose glomérulaire et les croissants cellulaires avaient un effet synergistique qui augmentait l'information pronostique obtenue à partir de l'analyse de l'atrophie tubulaire seule. Ainsi, l'apparition simultanée d'une atrophie tubulaire, d'une sclérose glomérulaire et de croissants cellulaires identifiait à un groupe à très haut risque; six de neuf malades ont progressé vers une néphropathie terminale dans les quatre ans suivant l'entrée dans l'étude. En conclusion, un score semiquantitatif des caractéristiques histologiques individuelles peut raffiner les estimations du risque d'insuffisance rénale chez des malades lupiques atteints de DPGN ou de MPGN.

The highly variable nature of lupus nephritis has prompted investigation of prognostic features that would permit identification of those at high risk of renal failure. The renal histologic classification system described by Pollak, Pirani, and Kark [1], and Pollak, Pirani, and Schwartz [2] and later modified by Baldwin et al [3] was an important contribution; diffuse proliferative glomerulonephritis (DPGN) appeared to be a particularly ominous finding. While some investigators concur that DPGN is a strong prognostic indicator [1–8], others have not confirmed this observation [9–15]. The variable clinical outcomes of

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patients with DPGN weaken the predictive value of this classification and reflect, in part, the pathologic heterogeneity encountered within this subgroup [16, 17]. Recognition of DPGN is based primarily on the extent of endocapillary proliferation but also incorporates features of necrosis, sclerosis, and capillary loop thickening.

The clinical course of patients with DPGN is probably influenced by the variable occurrence of certain histologic features not specified by the conventional classification system of lupus nephritis. Thus, detailed description of active and chronic, irreversible pathologic lesions affecting glomeruli, tubules, interstitium, and vasculature could augment the prognostic information derived from histologic classification and permit recognition of those patients with DPGN at high risk of end-stage renal disease.

To address this issue, a semiquantitative scoring system was used to examine the prognostic value of individual types of histologic lesions as well as of composites of activity and chronicity features of renal biopsy specimens among patients with DPGN and membranoproliferative glomerulonephritis (MPGN).

Methods

Early histologic predictors of renal failure were sought among 111 entrants into long-term prospective therapeutic trials of lupus nephritis at the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) from 1969 to 1980. Prerandomization renal biopsy specimens adequate for detailed light microscopic examination were available on 102 patients who were thus included in the present analysis. The clinical studies have been reported elsewhere [18–23]. Admission criteria included: *(1)* a diagnosis of systemic lupus erythematosus as specified by the American Rheumatism Association [24]; *(2)* reproducible clinical evidence of active glomerulonephritis; *(3)* creatinine clearance greater than 20 ml/min; *(4)* no cytotoxic drug therapy within 8 weeks prior to potential study entry; and *(5)* informed consent to all aspects of the study. For their own protection, patients with any one of the following were excluded from a therapeutic trial: *(1)* major infection within 2 weeks, *(2)* pregnancy, or *(3)* sensitivity to a study drug.

Renal histology

Specimen preparation. For light microscopy, specimens were fixed in B5 (buffered formaldehyde-mercuric chloride) solution for 2 to 4 hr and paraffin-embedded tissue was cut at 4 μ. Conventional hematoxylin-eosin, periodic acid Schiff (PAS), and Masson's trichrome stains were utilized. For electron microscopy, tissue samples were fixed in 2.5% buffered glutaraldehyde, postfixed in 1% osmium tetroxide, dehydrated in graded alcohol, and embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate.

Conventional classification. World Health Organization (WHO) criteria were used for the light microscopy classification of the major forms of lupus nephritis [25]. Briefly, DPGN was recognized by combinations of endocapillary proliferation, necrosis, sclerosis, and capillary loop thickening in more than 50% of glomeruli. The subset of biopsy specimens with MPGN exhibited diffuse lobular hypercellularity with a narrowing of capillary lumina and/or subendothelial mesangial extension causing double contours.

Refinement of the description of biopsy specimens within the pathologic spectrum of DPGN and MPGN was approached using a modification of a previously reported system [26] involving semiquantitative scoring of specific biopsy features to be described individually below. A scale of 0, 1, 2, or 3+ applied to each item generally corresponded to absent, mild, moderate and severe, respectively, for biopsy specimens in which six or more glomeruli were examined. The nephropathologist and the nephrologist independently graded the morphologic alterations without knowledge of the patients' clinical course. Consistent with previous experience [27, 28], assigned scores rarely differed by more than one point. Discrepancies were resolved by arbitrarily employing the higher grade.

Glomerular cell proliferation. This feature indicated the degree of glomerular endocapillary hypercellularity (mesangial, endothelial, and possibly infiltrating monocytes) leading to reduction of circulatory volume of glomerular capillary loops. The lesions were scored by the extent of loss of circulatory space due to segmental (or global) proliferative changes in less than 25% (1+), 25 to 50% (2+), or greater than 50% (3+) of glomeruli.

Leucocyte exudation. Exudation of more than two polymorphonuclear leucocytes per glomerulus was considered abnormal. Exudation was scored as mild (1+), moderate (2+), or extensive (3+).

Karyorrhexis and fibrinoid necrosis. Karyorrhexis was defined by the presence of pyknotic and fragmented nuclei. Fibrinoid necrosis was identified by the occurrence of intensely eosinophilic material within solidified segments of glomeruli. Fibrinoid necrosis was usually confirmed by Masson stain and was typically accompanied by karyorrhexis in involved glomeruli. The following scale of severity was used: karyorrhexis only or fibrinoid necrosis in less than 25% of glomeruli (1+), fibrinoid necrosis in 25 to 50% (2+) or greater than 50% (3+) of glomeruli. The assigned score was weighted by a factor of two [2] because such lesions were considered to be disproportionately severe as previously suggested [29].

Cellular crescents. Proliferating extracapillary cells occupying one-fourth or more of the glomerular capsular circumference were considered cellular crescents. Determination of the predominant component of crescents (cellular or fibrous) was assisted by Masson staining. The crescent score was defined as follows: cellular crescents in less than 25% (1+), 25 to 50% (2+), or greater than 50% (3+) of glomeruli. The assigned score was weighted by a factor of two [2] because such lesions were considered to be disproportionately severe [29].

Hyaline deposits. Eosinophilic material of a homogenous consistency along the circumference of the luminal surface of glomerular capillaries constituted the classical wire loop lesion. More extensive globular material occupying entire capillary loops were identified as hyaline thrombi. The hyaline material was considered to represent massive accumulation of immune complexes. Hyaline lesions were scored as few (1+), moderate (2+), or extensive (3+).

Interstitial inflammation. Infiltration of mononuclear cells (lymphocytes, plasma cells, macrophages) into interstitial spaces was assigned scores of mild (1+), moderate (2+), or extensive (3+).

Glomerular sclerosis. Glomerular capillary collapse with attendant expansion of mesangial matrix material and subse-

quent solidification was observed in both segmental and global patterns. Solidification occurring only segmentally or in global patterns in less than 25% (1+) of glomeruli, and global sclerosis in 25 to 50% (2+) or greater than 50% (3+) of glomeruli were designated.

Fibrous crescents. Structures composed predominantly or exclusively of fibrous tissue lining Bowman's capsule in a circumferential pattern were considered fibrous crescents. The crescent scores were defined as follows: fibrous crescents in less than 25% (1+), 25 to 50% (2+) or greater than 50% (3+) of glomeruli.

Tubular atrophy. Atrophic changes were identified by the thickening of tubular basement membranes, with or without tubular epithelial cell degeneration. Separation of residual tubules was typically observed. The severity of tubular atrophy was designated as mild (1+), moderate (2+), or extensive (3+).

Interstitial fibrosis. The deposition of periglomerular and peritubular fibrous tissue was judged primarily by the Masson stain. The severity of interstitial fibrosis was designated as mild (1+), moderate (2+), or extensive (3+).

Activity Index (AI). This index was defined as the sum of individual scores of the following items considered to represent measures of active lupus nephritis: glomerular proliferation, leucocyte exudation, karyorrhexis/fibrinoid necrosis (×2), cellular crescents (×2), hyaline deposits, and interstitial inflammation. The maximum score was 24 points for the Activity Index.

Chronicity Index (CI). This index consisted of the sum of individual scores of the following items considered to represent measures of chronic irreversible lupus nephritis: glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis. The maximum score was 12 points for the Chronicity Index.

Electron microscopy. Generally two or three glomeruli were examined in each biopsy specimen. For the present study the location and extent of electron dense deposits were quantitated on a scale of 0 to 4+, corresponding to a range of absent to massive. The deposits present in each of the following five locations were individually scored: mesangial, subendothelial, subepithelial, intramembranous, and extraglomerular (peritubular and/or perivascular). In addition to immune deposit analysis, the presence or absence of tubuloreticular structures was noted in endothelial cells.

Statistical analysis

To determine the predictive value of various histologic features, computer-assisted survival analysis used the time interval from study entry to endstage renal disease as the measure of outcome. Since the precise time to failure is unknown for those who have yet to experience the terminal event, statistical methods appropriate for the analysis of censored data were used [30–32].

Light and electron microscopic features were individually tested for prognostic significance using renal failure rate as the criterion (Table 1). This rate was defined as the number of renal failures per 1000 patient-months of observation. The renal failure rate was calculated at each level of pathologic variables, and contiguous subgroups with similar failure rates were combined. The prognostic value of variables subdivided into three or more groups was determined by the "score test" of trend [33], which is similar to a test for the trend in a simple linear regression. For variables with only two levels, the trend test simplifies to one similar to a Student's t test of means.

The predictive value of various histologic features of lupus nephritis was further examined by cumulative survival curves derived by the Kaplan-Meier method [34]. Thus, the estimate of survival probability was recalculated at each unique time of renal failure. The equality of survival curves obtained for different subgroups of patients was tested employing two statistics appropriate for censored data: the Gehan [35] and the Mantel-Haenszel [36]. The Gehan test is more sensitive to early failures than the Mantel-Haenszel test.

Results

Histologic features of lupus nephritis were examined in 102 patients in an attempt to identify early prognostic indicators of renal failure (median follow-up, 53 months). At study entry, the median age was 27 years, and lupus nephritis had been clinically evident for a median of 9 months. There were 15 males and 87 females. Employing WHO histologic criteria, the prerandomization renal biopsy specimens were classified as follows: 60 diffuse proliferative (DPGN), 12 membranoproliferative (MPGN), 7 focal proliferative, 16 membranous, and 7 mesangial glomerulonephritis.

All 11 patients experiencing renal failure were among the 72 patients who had DPGN (ten failures) or MPGN (one failure); hence this combined group was at modestly, but significantly, increased risk of endstage renal disease compared to those with focal proliferative, membranous, or mesangial glomerulonephritis (Fig. 1). However, the infrequent occurrence of renal failure among patients with DPGN or MPGN weakens these classifications as prognostic indicators. Thus, analyses were done to determine which patients with DPGN or MPGN were at high risk of renal failure. The predictive value of individual histologic features, as well as composite scores, specified by Activity and Chronicity Indices, were examined in the 72 patients classified as having DPGN or MPGN.

Figure 2 illustrates the predictive value of extensive active histologic change. Patients with Activity Indices (AI) greater than or equal to 12 were at a significantly increased risk of endstage renal disease compared to those with lower Activity Indices. At the end of a 4-year observation, the estimated probability of renal failure outcome in the high risk group was 40% compared to 7% for the low risk group.

In contrast to AI, the Chronicity Index (CI) appeared to have a graded impact on prognosis permitting identification of patients with low, intermediate, and high rates of renal failure (Fig. 2). While endstage renal disease has yet to occur in the 29 patients with little or no chronic histologic change ($CI \leq 1$), the renal failure rate was significantly increased among patients with mid- or high-range Chronicity Indices.

To derive additional prognostic information from renal morphology, renal failure rates were calculated for groups with different types of individual histologic features as described in **Methods** (Table 1). In general, the composite AI was more strongly predictive than individual active features of the biopsy specimen. Patients with cellular crescents showed a moderate elevation of the renal failure rate. In addition, two of three patients with severe fibrinoid necrosis failed quickly (28 and 31 months). The four persons who failed either without cellular crescents or without fibrinoid necrosis all had chronic tubuloin-

Table 1. Renal failure rates by levels of prognostic factors for 72 patients with diffuse or membranoproliferative glomerulonephritis

Prognostic factor	Number[a]	Failures[b]	Rate[c]	*P*-value[d]	Prognostic factor	Number[a]	Failures[b]	Rate[c]	*P*-value[d]
Composite Pathologic Scores					Fibrous crescents				0.028
Activity Index[e]				0.048	None	55	6	1.68	
Low/mid	55	6	1.72		Mild/severe	17	5	5.86	
High	17	5	5.35		Tubular atrophy				0.004
Chronicity Index				0.0003	None	29	0	0.00	
Low	29	0	0.0		Mild/severe	43	11	4.41	
Mid	23	4	2.67		Interstitial fibrosis				0.004
High	20	7	7.25		None	26	1	0.52	
					Mild	36	6	3.03	
Individual light microscopy features					Mod/severe	10	4	7.50	
Proliferation				0.941	Electron microscopy deposits[f]				
None/mild	6	0	0.0		Mesangial				0.425
Moderate	55	10	2.84		Absent	1	0	0.0	
Severe	11	1	1.58		Mild	6	2	5.58	
Leucocytes				0.667	Moderate	17	3	3.00	
None	37	6	2.78		Extensive	21	2	1.76	
Mild	27	4	2.33		Massive	2	0	0.0	
Mod/severe	8	1	1.83		Subendothelial				0.337
Necrosis				0.858	Absent	17	3	3.09	
None	11	3	4.25		Mild	9	2	4.67	
Mild	34	4	1.90		Moderate	15	2	1.85	
Moderate	24	2	1.34		Extensive/massive	6	0	0.0	
Severe	3	2	16.26		Subepithelial				0.981
Cellular crescents				0.113	Absent	10	1	1.82	
None	43	4	1.56		Mild	15	3	2.98	
Mild	18	4	3.20		Moderate	14	2	2.96	
Mod/severe	11	3	4.84		Extensive	8	1	1.95	
Hyaline deposits				0.979	Intramembranous				0.284
None	29	5	2.65		Absent	21	2	1.49	
Mild	20	2	1.46		Mild/extensive	26	5	3.56	
Moderate	16	4	4.92		Extraglomerular deposits				0.306
Severe	7	0	0.0		Absent	32	4	1.97	
Interstitial Inflammation				0.972	Mild/moderate	15	3	4.22	
None	9	1	1.90		Tubuloreticular structures				0.517
Mild	34	5	2.78		Absent	14	3	3.47	
Mod/severe	29	5	2.38		Present	33	4	2.18	
Glomerular sclerosis				0.024					
None	43	4	1.42						
Mild	19	4	3.33						
Mod/severe	10	3	7.21						

[a] The number of patients with the specified level of a histologic variable are listed.
[b] The numbers listed reflect the numbers of patients progressing to renal failure in each pathologic subset.
[c] The renal failure rate equals the number of renal failures/1000 patient-months of follow-up (see *Statistical analysis*).
[d] The *P* value exhibits the significance level for the "score test" of equality or of the trend of renal failure rates (see *Statistical analysis*).
[e] Adjacent levels of a prognostic factor that have similar renal failure rates were combined.
[f] For each variable in this group there were 25 patients with unknown values; this group had four with renal failure with a rate of 2.38/1000 patient-months.

terstitial disease. Little prognostic information could be derived from the presence or extent of endocapillary proliferation, leucocytic exudation, or hyaline thrombi in glomeruli, or interstitial inflammation.

Different from the active histologic features, each individual chronic pathologic variable (glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis) was associated with an increased risk of endstage renal disease. Particularly striking was the predictive value of tubular atrophy. All 11 renal failures occurred among the 43 patients with this finding in prerandomization renal biopsy specimens. While tubular atrophy clearly identified a high-risk group, most of its members have yet to fail. Hence, additional individual histologic features were considered in an effort to enhance outcome predictions based on tubular atrophy alone. Relatively strong prognostic indicators affecting glomeruli (Table 1) were tested for predictive value in the tubular atrophy group using the renal failure rate as the criterion (interstitial fibrosis was nearly always associated with tubular atrophy and thus contributed little additional prognostic information). Cellular crescents, glomerular sclerosis, and fibrous crescents were examined individually and in pair combinations as dichotomous variables. Considered individually, the three variables failed to improve outcome prediction for patients manifesting tubular atrophy. On the other hand, the simultaneous occurrence of cellular crescents and glomerular sclerosis placed patients with tubular atrophy at a particularly high risk of renal failure (Fig. 3 [37]). Thus, in the presence of tubular atrophy, the combination of cellular crescents and glomerular sclerosis had a synergistic impact on outcome. While this interaction was recognized employing

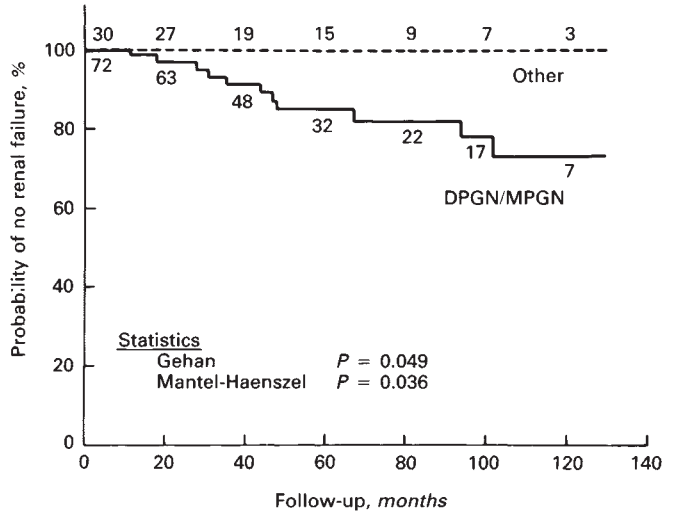

Fig. 1. *Cumulative survival curves demonstrating the probability of maintaining life-supporting renal function in patients with diffuse proliferative or membranoproliferative lupus nephritis* (DPGN/MPGN) *compared to other patients with focal proliferative, membranous, or mesangial lupus nephritis* (Other). *Numbers* on the *curves* indicate the number of patients in the group that remains at risk.

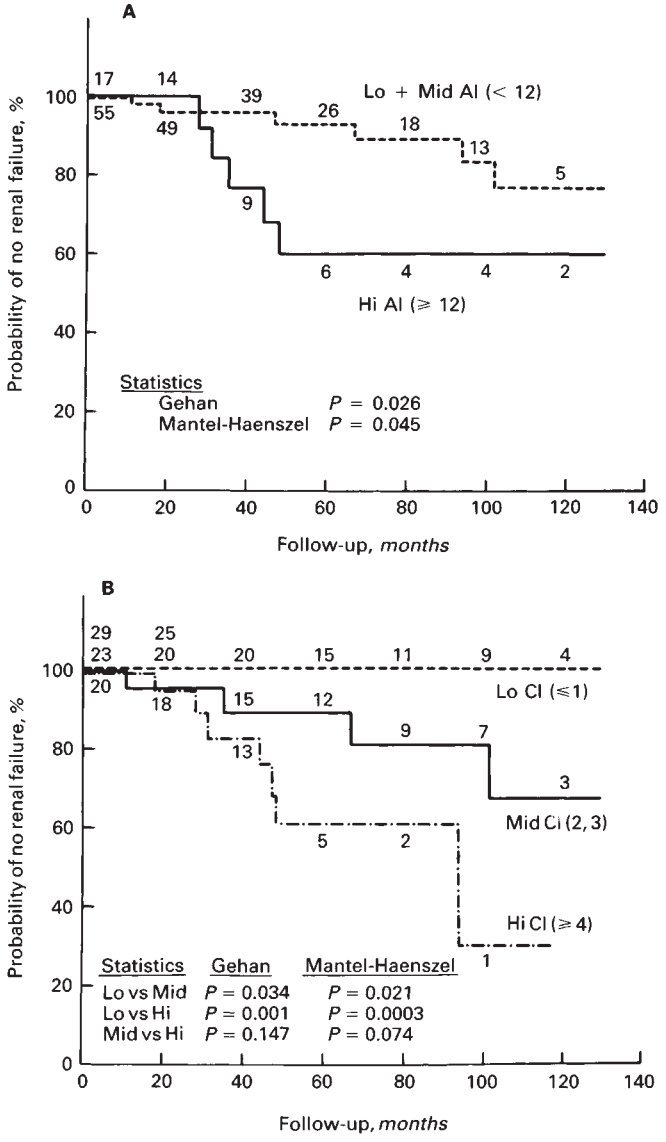

Fig. 2. *Cumulative survival curves based on 72 lupus patients with DPGN or MPGN demonstrating the prognostic impact of the Activity* (AI) *and Chronicity* (CI) *Indices on the probability of maintaining life-sustaining renal function. Numbers* on the *curves* indicate the number of patients in the group that remains at risk. For calculation of AI, cellular crescents and necrosis were weighted by a factor of two. [A composite activity score derived ascribing equal weight to all active histologic features revealed similar prognostic information; a score greater than or equal to ten identified patients at an increased risk of renal failure compared to those with lower scores (Gehan, $P = 0.023$; Mantel-Haenszel, $P = 0.038$).]

relatively uncomplicated statistical methods, the Cox multivariate survival analysis [38] confirmed the observation (details not included).

Figure 3 depicts cumulative survival curves for DPGN/MPGN patients with the combination of tubular atrophy, cellular crescents, and glomerular sclerosis ($N = 9$) compared to all other DPGN/MPGN patients who lacked such a combination of unfavorable prognostic features ($N = 63$). Six of nine persons affected by all three factors progressed to endstage renal disease within 4 years, resulting in significantly different renal function survival probabilities for groups defined in this manner. Because of the a posteriori manner in which the groups were selected, the significance levels portrayed in Figure 3 should be interpreted cautiously.

The prognostic information derived from electron microscopy was limited in part by the lack of data for 25 patients, including four who progressed to renal failure. Of the electron microscopic features depicted in Table 1, intramembranous deposits (IM) appeared most informative, and further analysis of each electron microscopic variable employing cumulative survival curves confirmed this impression. Of interest, all five patients with renal failure in the IM subgroup failed within 4 years of study entry, whereas the two in the non-IM subgroup developed after longer follow-up periods (67 and 94 months). Using the Gehan test, which is relatively more sensitive to early events, suggestive evidence was obtained that patients with intramembranous deposits were at an increased risk of early renal failure outcome ($P = 0.083$). Noteworthy is the association between scores of intramembranous deposits and of glomerular sclerosis (Pearson chi-square, $\chi^2 = 13.27$, 6 df, $P = 0.039$).

Discussion

The present study examined the hypothesis that semiquantitative scoring of individual histologic features of lupus nephritis could augment the prognostic information obtained by renal pathology classification. While conventional classification schemes yield valuable information, it is inevitable that differences among patients will be obscured by categorizing the diverse histologic lesions of lupus nephritis into a small number of classes. The system lacks sufficient flexibility and detail to describe completely the highly variable renal pathology encountered [16, 17]. The problem is particularly striking among patients classified as having DPGN or MPGN, wherein the same histologic label is applied to an especially broad range of

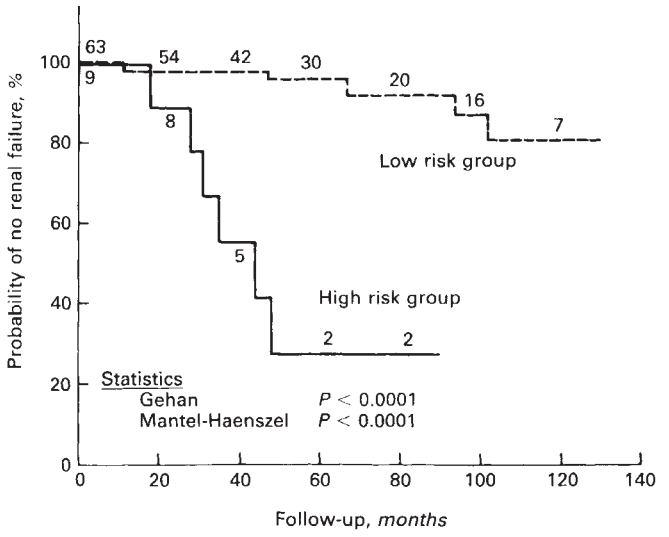

Fig. 3. *Cumulative survival curves based on 72 lupus patients with DPGN or MPGN demonstrating the probability of maintaining life-supporting renal function in high- and low-risk groups identified according to the individual histologic features tubular atrophy, glomerular sclerosis, and cellular crescents.* The high-risk group consists of individuals whose prerandomization renal biopsy specimens reflected the presence of all three pathologic variables. Survival estimates are subject to increased error when few patients remain under observation indicated by *numbers on the curves*. The 95% confidence limits for the high-risk group were (0.365, 0.939), (0.204, 0.805), and (0.051, 0.576) at 24, 36, and 48 months, respectively [37].

active and of chronic, irreversible pathologic lesions affecting glomeruli, tubules, interstitium, and vasculature.

The diversity of clinical course observed among patients with DPGN or MPGN underscores the need to search for prognostic indicators that could enhance outcome predictions based solely on renal histologic classification. Similar to previous observations [1–8], our patients with DPGN or MPGN were at a significantly increased risk of endstage renal disease compared to those with focal proliferative, membranous, or mesangial glomerulonephritis. Nonetheless, the relatively low incidence of renal failure outcome observed in patients with DPGN or MPGN limits the predictive value of these classifications. Thus, it is not surprising that efforts to use renal histologic classification as a prognostic tool have led to variable results [1–15].

A number of investigators have employed semiquantitative scoring systems to provide detailed descriptions of the diverse pathology encountered in lupus nephritis [1, 2, 8, 10, 13, 15, 27–29, 39–44]. Using such a system, the present study emphasizes the prognostic value of specific morphologic attributes other than the conventional classification. Among patients with DPGN or MPGN, individual histologic features recorded at study entry as well as the composite scores, AI and CI, were studied by computer-assisted survival analysis using time to renal failure as the measure of outcome.

Particularly striking was the predictive value of sclerosing lesions. CI had a graded impact on prognosis, and each individual chronic histologic feature was associated with an increased risk of endstage renal disease. The adverse prognostic impact of irreversible parenchymal destruction extends previous observations [13, 15, 29, 40].

Similarly, severely active pathologic change, reflected by marked elevations in AI, cellular crescents, and severe fibrinoid necrosis, foretold an unfavorable outcome. We suggest that these results indicate a tendency for such fulminant active lesions to be associated with subsequent sclerosis and permanent loss of functional renal tissue. Other, less severe, active lesions are potentially reversible and thus, may be relatively weak predictors of long-term renal function outcome.

Among the individual histologic variables tested for prognostic significance, tubular atrophy emerged as particularly important. All 11 renal failures occurred among the 43 patients manifesting tubular atrophy on prerandomization renal biopsy specimen. While this morphologic attribute clearly identified a high-risk group, outcome predictions could be enhanced by the simultaneous consideration of glomerular sclerosis and cellular crescents as well as tubular atrophy. Six of nine patients with all three adverse prognostic indicators progressed to endstage renal disease within 4 years. Thus, the presence of chronic, irreversible lesions affecting both the glomerular and the tubular portions of the nephron, plus the relatively ominous active feature, cellular crescents, identified particularly high-risk patients.

It is of interest that tubular atrophy was such a strong prognosticator that consideration of additional single pathologic variables failed to enhance outcome predictions among patients with tubular atrophy. However, examination for interactions among variables revealed that glomerular sclerosis and cellular crescents had a synergistic impact which amplified the prognostic information based on tubular atrophy alone. Therefore, in the presence of tubular atrophy, the simultaneous occurrence of severe active (cellular crescents) as well as chronic, irreversible glomerular lesions (sclerosis) was of considerable prognostic significance.

Efforts to derive prognostic information from electron microscopy were hampered, in part, by incomplete data. Of the features examined, intramembranous deposits were modestly associated with increased risk of early renal failure outcome. Considering the proposed evolution of these deposits [45] and their association with glomerular sclerosis in this study, they appear to represent an electron microscopic expression of chronic pathologic change.

In sum, evidence is presented supporting the hypothesis that semiquantitative scoring of individual histologic features can augment prognostic information derived from conventional classification. Thus, certain heretofore little used morphologic attributes can refine estimates of renal failure risks in patients with DPGN or MPGN.

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References

1. Pollak VE, Pirani CL, Kark RM: Effect of large doses of prednisone on the renal lesions and life span of patients with lupus glomerulonephritis. *J Lab Clin Med* 57:495–511, 1961

2. POLLAK VE, PIRANI CL, SCHWARTZ FD: The natural history of the renal manifestations of systemic lupus erythematosus. *J Lab Clin Med* 63:537–550, 1964
3. BALDWIN DS, LOWENSTEIN J, ROTHFIELD NF, GALLO G, MCCLUSKEY RT: The clinical course of the proliferative and membranous forms of lupus nephritis. *Ann Intern Med* 73:929–942, 1970
4. ZWEIMAN B, KORNBLUM J, CORNOG J, HILDRETH EA: The prognosis of lupus nephritis. Role of clinical-pathologic correlations. *Ann Intern Med* 69:441–453, 1968
5. ESTES D, CHRISTIAN CL: The natural history of systemic lupus erythematosus by prospective analysis. *Medicine* 50:85–95, 1971
6. CHEATUM DE, HURD ER, STRUNK SW, ZIFF M: Renal histology and clinical course of systemic lupus erythematosus: a prospective study. *Arthritis Rheum* 16:670–676, 1973
7. BALDWIN DS, GLUCK MC, LOWENSTEIN J, GALLO G: Lupus nephritis: clinical course as related to morphologic forms and their transitions. *Am J Med* 62:12–30, 1977
8. APPEL GB, SILVA FG, PIRANI CL, MELTZER JI, ESTES D: Renal involvement in systemic lupus erythematosus (SLE): a study of 56 patients emphasizing histologic classification. *Medicine* 57:371–410, 1978
9. HECHT B, SIEGEL N, ADLER M, KASHGARIAN M, HAYSLETT JP: Prognostic indices in lupus nephritis. *Medicine* 55:163–181, 1976
10. FISH AJ, BLAU EB, WESTBERG NG, BURKE BA, VERNIER RL, MICHAEL AF: Systemic lupus erythematosus within the first two decades of life. *Am J Med* 62:99–117, 1977
11. FRIES JF, PORTA J, LIANG MH: Marginal benefit of renal biopsy in systemic lupus erythematosus. *Arch Intern Med* 138:1386–1389, 1978
12. CAMERON JS, TURNER DR, OGG CS, WILLIAMS DG, LESSOF MH, CHANTLER C, LEIBOWITZ S: Systemic lupus with nephritis: a long-term study. *Q J Med* 48:1–24, 1979
13. BALLOU S, CHUNG-PARK M, WAGGONER DM, KUSHNER I: Prognostic value of clinical and renal biopsy findings in lupus nephritis *(abstract). Clin Res* 28:339A, 1980
14. WALLACE DJ, PODELL TE, WEINER JM, COX MB, KLINENBERG JR, FOROUZESH S, DUBOIS EL: Lupus nephritis: experience with 230 patients in a private practice from 1950 to 1980. *Am J Med* 72:209–220, 1982
15. WHITING-O'KEEFE Q, HENKE JE, SHEARN MA, HOPPER J, BIAVA CG, EPSTEIN WV: The information content from renal biopsy in systemic lupus erythematosus: step-wise linear regression analysis. *Ann Intern Med* 96:718–723, 1982
16. DECKER JL, STEINBERG AD, REINERTSEN JL, PLOTZ PH, BALOW JE, KLIPPEL JH: Systemic lupus erythematosus: evolving concepts. *Ann Intern Med* 91:587–604, 1979
17. BALOW JE: Therapeutic trials in lupus nephritis: problems related to renal histology, monitoring of therapy and measures of outcome. *Nephron* 27:171–176, 1981
18. STEINBERG AD, KALTREIDER HB, STAPLES PJ, GOETZL EJ, TALAL N, DECKER JL: Cyclophosphamide in lupus nephritis: a controlled trial. *Ann Intern Med* 75:165–171, 1971
19. STEINBERG AD, DECKER JL: A double-blind controlled trial comparing cyclophosphamide, azathioprine and placebo in treatment of lupus glomerulonephritis. *Arthritis Rheum* 17:923–937, 1974
20. DECKER JL, KLIPPEL JH, PLOTZ PH, STEINBERG AD: Cyclophosphamide or azathioprine in lupus glomerulonephritis: a controlled trial: results at 28 months. *Ann Intern Med* 83:606–615, 1975
21. DINANT HJ, DECKER JL, KLIPPEL JH, BALOW JE, PLOTZ PH, STEINBERG AD: Alternative modes of cyclophosphamide and azathioprine therapy in lupus nephritis. *Ann Intern Med* 96:728–736, 1982
22. CARETTE S, KLIPPEL JH, DECKER JL, AUSTIN HA, PLOTZ PH, STEINBERG AD, BALOW JE: Controlled studies of oral immunosuppressive drugs in lupus nephritis: a long-term follow-up. *Ann Intern Med* 99:1–8, 1983
23. AUSTIN HA, MUENZ LR, JOYCE KM, ANTONOVYCH TT, KULLICK ME, KLIPPEL JH, DECKER JL, BALOW JE: Prognostic factors in lupus nephritis: contribution of renal histology. *Am J Med* 75:382–391, 1983
24. COHEN AS, REYNOLDS WE, FRANKLIN EC, KULKA JP, ROPES MW, SHULMAN LE, WALLACE SL: Preliminary criteria for the classification of systemic lupus erythematosus. *Bull Rheum Dis* 21:643–648, 1971
25. MCCLUSKEY RT: Lupus nephritis, in *Pathology Decennial,* edited by SOMMERS SC, New York, Appleton-Century-Crofts, 1975, pp 435–460
26. PIRANI CL, SALINAS-MADRIGAL L: Evaluation of percutaneous renal biopsy. *Pathol Annu* 3:249–296, 1968
27. PIRANI CL, POLLAK VE, SCHWARTZ FD: The reproducibility of semiquantitative analyses of renal histology. *Nephron* 1:230–237, 1964
28. DONADIO JV, HOLLEY KE, WAGONER RD, FERGUSON RH, MCDUFFIE FC: Treatment of lupus nephritis with prednisone and combined prednisone and azathioprine. *Ann Intern Med* 77:829–835, 1972
29. MOREL-MAROGER L, MERY JP, DROZ D, GODIN M, VERROUST P, KOURILSKY O, RICHET G: The course of lupus nephritis: contribution of serial renal biopsies. *Adv Nephrol* 6:79–118, 1976
30. PETO R, PIKE MC, ARMITAGE P, BRESLOW NE, COX DR, HOWARD SV, MANTEL N, MCPHERSON K, PETO J, SMITH PG: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 34:585–612, 1976
31. PETO R, PIKE MC, ARMITAGE P, BRESLOW NE, COX DR, HOWARD SV, MANTEL N, MCPHERSON K, PETO J, SMITH PG: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 35:1–39, 1977
32. LEE EL: *Statistical Methods for Survival Data Analysis.* Belmont, California, Wadsworth, 1980, pp 75–154
33. COX DR, HINKLEY DV: *Theoretical Statistics.* London, Chapman and Hall, 1974, p 315
34. KAPLAN EL, MEIER P: Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 53:457–481, 1958
35. GEHAN EA: A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. *Biometrika* 52:203–223, 1965
36. MANTEL N: Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 50:163–170, 1966
37. KALBFLEISCH JD, PRENTICE RL: *The Statistical Analysis of Failure Time Data.* New York, John Wiley and Sons, 1980, p 15
38. COX DR: Regression models and life tables (with discussion). *J Royal Stat Soc, Series B* 34:187–220, 1972
39. MUEHRCKE RC, KARK RM, PIRANI CL, POLLAK VE: Lupus nephritis: a clinical and pathological study based on renal biopsies. *Medicine* 35:1–145, 1957
40. STRIKER GE, KELLY MR, QUADRACCI LJ, SCRIBNER BH: The course of lupus nephritis: a clinical-pathological correlation of fifty patients, in *Glomerulonephritis,* edited by KINCAID-SMITH P, MATHEW T, BECKER EL, New York, John Wiley and Sons, 1973, pp 1141–1166
41. MAHAJAN SK, ORDONEZ NG, SPARGO BH, KATZ AI: Changing histopathology patterns in lupus nephropathy. *Clin Nephrol* 10:1–8, 1978
42. COMERFORD RF, COHEN AS: The nephropathy of systemic lupus erythematosus: an assessment by clinical, light and electron microscopic criteria. *Medicine* 46:425–473, 1967
43. NANRA RS, KINCAID-SMITH P: Lupus nephritis: clinical course in relation to treatment, in *Glomerulonephritis,* edited by KINCAID-SMITH P, MATHEW TH, BECKER EL, New York, John Wiley and Sons, 1973, pp 1193–1210
44. HILL GS, HINGLAIS N, TRON F, BACH J-F: Systemic lupus erythematosus: morphologic correlations with immunologic and clinical data at the time of biopsy. *Am J Med* 64:61–79, 1978
45. EHRENREICH J, CHURG J: Pathology of membranous nephropathy. *Pathol Ann* 3:145–186, 1968